HIV Within-Host Dynamics Incorporating Cell to Cell Virus Transmission

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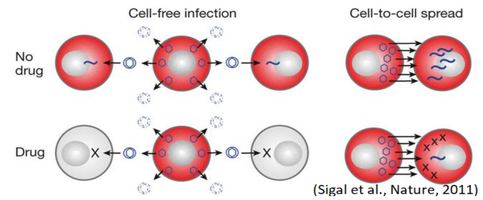
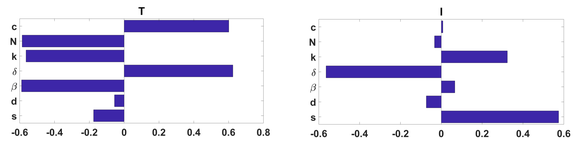
Abstract

HIV can be directly transmitted from infected cells to healthy cells. In this project, a new HIV model is developed by including both cell-to-cell transmission and cell-free virus infection. Basic reproductive number R_0 is obtained and shown to be a critical threshold parameter. Two steady states of the model are obtained and the corresponding characteristic equations are analyzed. It is shown that the infection-free steady state is locally asymptotically stable when R_0 lies below unity while the infected steady state is locally asymptotically stable when R_0 exceeds unity. Sensitivity and uncertainty analysis was performed to evaluate which parameter(s) the model prediction and R_0 are most sensitive to. During cell-to-cell transmission, multiple virions can be transmitted simultanenously, which makes the therapy difficult to inhibit all the transmission. An extended model including different numbers of virions transmitted during cell-to-cell transmission has been proposed and will be further analyzed to study the HIV dynamics under therapy.

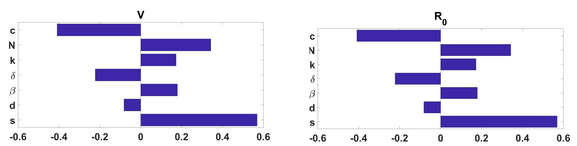
Cell-to-cell transmission



PRCC results



PRCC of T and I

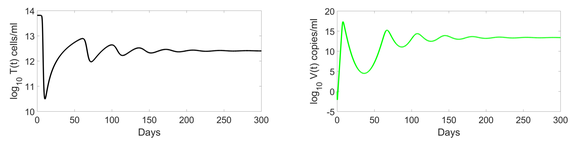


PRCC of V and R_0

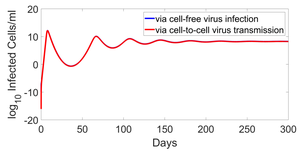
Variable & Parameter

Par.	Description	Value
$T(t)$	$CD4^+$ uninfected cells	cells
$T^*(t)$	$CD4^+$ infected cells via cell-free infection	cells
$I(t)$	$CD4^+$ infected cells via cell-to-cell	cells
$V(t)$	Population of virus	virus
s	Generation rate of uninfected cells	$10^4 \frac{1}{mL.day}$
d	Death rate of uninfected cells	0.01 per day
β	Infection rate of cells by cell-free virus	$2.4 \times 10^{-8} \frac{mL}{day}$
k	Rate of cell-to-cell viral transmission	$2 \times 10^{-6} \frac{mL}{day}$
δ	Death rate of infected cells	1 per day
N	Viral burst size	$2 \times 10^3 \frac{virus}{cell}$
c	Viral clearance rate	23 per day

Simulation of dynamics



Predicted dynamics of $T(t)$ and $V(t)$

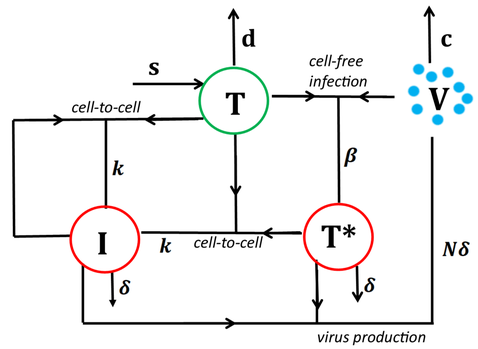


Predicted dynamics of $T^*(t)$ and $I(t)$

Conclusion

We developed and analyzed a new HIV infection model that includes both cell-free virus infection and cell-to-cell transmission. The basic reproductive ratio is obtained and shown to govern the dynamics of the model. The extended model that includes different numbers of virions transmitted during cell-to-cell transmission may explain HIV persistence during suppressive therapy.

Viral Dynamic Model



R_0 is the number of new virions that can be produced by one virion put in a wholly susceptible $CD4^+$ T cell population.

By the Next Generation Matrix (**NGM**) method, we get

$$R_0 = \rho(\mathbf{NGM}) = \frac{\beta\, sN}{cd} + \frac{ks}{d\delta}$$

Proposition 0.1. *E_0 is locally asymptotically stable when $R_0 < 1$.*

Proposed Model :

$$\begin{aligned} \dot{T} &= s - dT - \beta TV - kT(T^* + I) \\ \dot{T^*} &= \beta TV - \delta T^* \\ \dot{I} &= kT(T^* + I) - \delta I \\ \dot{V} &= N\delta\,(I + T^*) - cV \end{aligned} \tag{1}$$

with non-negative initial condition

$$T(0) = T_0, T^*(0) = T_0^*, I(0) = I_0, V(0) = V_0$$

System (1) has two equilibria

- Infection free equilibrium
  $E_0 = (T_0 = \frac{s}{d}, T_0^* = 0, I_0 = 0, V_0 = 0)$
- Infected equilibrium, $E_1 = (T_1, T_1^*, I_1, V_1)$ where

$$\begin{aligned} T_1 &= \frac{\delta\, c}{N\beta\,\delta + ck} \quad ; \quad T_1^* = \frac{(R_0-1)cd\delta N\beta}{(N\beta\delta+ck)^2}; \\ I_1 &= \frac{c^2 kd(R_0-1)}{(N\beta\delta+ck)^2} \quad ; \quad V_1 = \frac{(R_0-1)d\delta N}{N\beta\delta+ck} \end{aligned}$$

Proposition 0.2. *E_1 exists and is locally asymptotically stable when $R_0 > 1$.*

An Extended Model Under Theraphy

$$\begin{aligned} \dot{T} &= s - dT - (1-\varepsilon)\beta TV - \sum_{i=1}^{n}(1-\varepsilon_i) f_i kT(T^* + \sum_{i=1}^{n} I_i) \\ \dot{T^*} &= (1-\varepsilon)\beta TV - \delta T^* \\ \dot{I}_i &= (1-\varepsilon_i) f_i kT(T^* + \sum_{i=1}^{n} I_i) - \delta_i I_i, \qquad i = 1, ..n \\ \dot{V} &= N\left(\delta T^* + \sum_{i=1}^{n} \delta_i I_i\right) - cV \end{aligned}$$

- I_i is the concentration of infected cells via cell-to-cell transmission in which i virions are transmitted
- ε is the drug efficacy blocking cell-free virus infection; ε_i is the drug efficacy blocking cell-to-cell transmission that leads to I_i
- $\varepsilon_1 > \varepsilon_2 > ... > \varepsilon_n$ (the more virions transmitted, the less effective therapy)
- $\sum_{i=1}^{n} f_i = 1$

The basic reproduction ratio for extended model under treatment is

$$R_0 = \tfrac{1}{2} T_0 \left(\frac{N\beta(1-\varepsilon)}{c} + k\sum_{i=1}^{n} \frac{(1-\varepsilon_i) f_i}{\delta_i} + \sqrt{\left(\frac{N\beta(1-\varepsilon)}{c} - k\sum_{i=1}^{n} \frac{(1-\varepsilon_i) f_i}{\delta_i} \right)^2 + \frac{4N(1-\varepsilon)\beta k}{c\delta} \sum_{i=1}^{n} (1-\varepsilon_i) f_i} \right)$$

References

Wang & Rong (2019). HIV low viral load persistence under treatment : Insights from a model of cell-to-cell viral transmission *Applied Mathematical Modelling*, 94:44-51, 2019.

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